IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Eugene H. Gans	:	Attorney Docket No.: 98-40012-US
Serial No.: Unknown	:	
Filed: February 19, 1998	:	
For: METHOD FOR THE TREATMENT OF ACNE	:	

NEW APPLICATION TRANSMITTAL

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Enclosed for filing is a new application for the above-entitled invention.

The application consists of:

7 pages of specification;
2 pages of claims;
1 page of abstract; and
0 sheets of formal drawings.

Also enclosed are:

1. a combined Declaration and Power of Attorney;
2. Assignment of the invention to Medicis Pharmaceutical Corporation;
3. a Recordation Cover Sheet Form PTO 1595; and
4. a check in the amount of $830.00.

EXPRESS MAIL CERTIFICATE (37 CFR 1.10)

Express Mail Label No. TB798520613US Date of Deposit Feb. 19, 1998

I hereby certify that this paper, and the papers and/or fees referred to herein as transmitted, submitted or enclosed, are being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Name William J. McNichol, Jr. Signature

The filing fees enclosed are calculated as below:

	Claim Count		No. Extra		Rate	
Total Claims	9	-20 =	0	x	22.00	0
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A check in the amount of $830.00 is enclosed in payment of the $790.00 basic filing fee and $40.00 assignment recordal fee.

The Commissioner is hereby authorized to charge any deficiency of the enclosed amount or credit any overpayment of any filing fees or fees for presentation of extra claims under 37 CFR 1.16 in connection with this transmittal to Deposit Account No. 18-0586. This paper is enclosed is duplicate.

Respectfully submitted,

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Dated: February 19, 1998

METHOD FOR THE TREATMENT OF ACNE

Field of the Invention

This invention relates to methods for the treatment of acne, and in particular to methods for the treatment of acne involving the use of oral tetracycline antibiotics.

Background of the Invention

Oral tetracycline antibiotics are frequently used in the treatment of acne. One of the most effective oral tetracycline antibiotics used in the treatment of acne it is minocycline. All tetracycline antibiotics are known to have some side effects. These side effects include vestibular symptoms such as vertigo, dizziness or blurred vision. These effects are sometimes disabling. See, Gould & Brookler, Arch. Otolarang. Vol. 96, p. 291 (1972); Williams et al., Lancet, Sept. 28, 1974, p. 144-45; Fanning & Gump, Arch. Intern. Med., Vol. 136, pp. 761-62 (1976). Headache and general malaise, along with gastro-intestinal symptoms such as the diarrhea, nausea, gas, or cramps also occur. Dry nose and dry mouth are also occasionally encountered.

Dosage forms of oral tetracycline antibiotics are typically constructed with a view towards achieving rapid dissolution rates. Rapid dissolution is believed to be essential to the effectiveness of these drugs. The driving force behind this practice is the understanding that rapid dissolution leads to rapid assimilation through the gut lining, where the antibiotics are then transmitted through the blood stream to the skin, where they are active against bacteria associated with acne. The United States Food and Drug Administration (FDA) has established standards for dissolution rates for various oral antibiotics. These standards set minimum

dissolution rates. For example, the FDA standard for oral minocycline is that 75 percent of the stated dosage must have dissolved within 45 minutes, under standard U.S. Pharmacopea test conditions. Commercial products are typically engineered to have a dissolution rates which are substantially faster than that required by the FDA. All of this is based upon the generally accepted belief in the art that, while dissolution rates enhance the effectiveness of the antibiotic, once the FDA minimum dissolution rate is achieved, all products have equivalent safety and efficacy.

Summary of the Invention

It has been discovered that the dissolution rate of oral tetracycline antibiotics, especially minocycline, can affect the occurrence of vestibular side effects. Specifically, too rapid dissolution of oral tetracyclines increases the incidence and severity of vestibular side effects. By reducing or slowing the dissolution rates of the antibiotics, the incidence and/or severity of vestibular side effects can be reduced significantly.

Detailed Description of the Invention

Vestibular reactions are an undesirable and sometimes seriously disconcerting side effect of minocycline therapy. According to the present invention, it is possible to provide persons susceptible to such side effects with the benefits of minocycline therapy while diminishing the incidence and/or severity of these side effects. This is accomplished by adjusting the dissolution rate of the minocycline in its dosage form so that, while an effective concentration of minocycline is achieved in the blood stream of the patient, vestibular side effects are greatly reduced.

In a preferred embodiment of the invention, the minocycline dissolves at a rate of only 15 percent within the first 15 minutes, 35 percent within 30 minutes, 50 percent within 45 minutes, and 80 percent within one hour. It is also advantageous to use a dissolution rate of 20 percent within 15 minutes, 50 percent in 30 minutes, 75 percent within 45 minutes and 100 percent dissolution within 60 minutes. Dissolution rates as fast as 30 percent within 15 minutes, 60 percent within 30 minutes, 75 percent within 45 minutes and complete dissolution within 60 minutes or even as fast as 35 percent within 15 minutes, 80 percent within 30 minutes and substantially complete dissolution within 45 minutes can be used. Preferred dissolution rates are within the range of 20 to 40 percent in 15 minutes, 50 to 80 percent in 30 minutes, and 70 to 95 percent in 45 minutes. Faster rates of 25 to 35 percent in 15 minutes, 60 to 80 percent in 30 minutes and 80 to 100 percent in 45 minutes are useful. It will be understood however, that the faster dissolution rates do not achieve as significant a reduction in the reduction of unwanted side effects as the slower dissolution rates.

Minocycline is available from a variety of sources. Various commercial products containing minocycline as their active ingredient have a variety of the dissolution rates. In the following example, slower dissolving minocycline is compared with fast-dissolving minocycline.

A blinded cross-over study of the vestibular side effects of minocycline involving 32 female subjects was conducted. The subjects were given either a fast dissolving or a slower dissolving dosage form of minocycline. The doses for the subjects were adjusted on the basis of each subject's total body weight and were in the range typically used for the treatment of severe acne. Subjects weighing 50 to 69 kg were given one-hundred milligrams. Subjects weighing 70 to 89 kg, the dose were given one hundred fifty milligrams and subjects above received 90

kilograms, 200 milligrams. This dose was given once a day at 5 p.m.. Subjects received one of the two dose forms for four days. After a two week washout, each group "crossed over" and received the dosage form that they had not received during the first four day period. Each subject was required to maintain an accurate diary of vestibular side effects. The diary recorded the number of days that each subject experienced vestibular side effects and the number of incidents of each symptom. The 32 subjects were evaluated over a five day period, yielding 160 person-day measurements per treatment group. The number of days that each subject recorded a side effect and the severity of that side effect the reported in Table 1.

From Table 1 it can be seen that a total of 27 incidents of vestibular side effects occurred in the fast dissolving treatment group, compared to only five incidents in the slower dissolving group. The severity of the vestibular side effects are reported on a scale of 1 to 4. With 1 indicating slight severity, 2 indicating mild severity, 3 moderate, and 4 severe side effects.

The dissolution rates for the fast dissolving dosage form and the slower dissolving dosage form are set forth below.

Table 1

Vestibular Side Effects

Patients Treated With Slower-Dissolving Minocycline

Symptom	Severity	No. of Time Intervals	Duration	Severity Category
dizziness	slight	2	8:00 am-4:00 pm	1
dizziness	slight-mild	4	all day	1.5
dizziness	mild	1	on and off	2
dizziness	slight	1	all evening	1
dizziness	slight-mild	2	morning thru mid day	1.5

Table 1 (contd.)

Patients Treated With Fast-Dissolving Minocycline

Symptom	Severity	No. of Time Intervals	Duration	Severity Category
dizziness	slight	2	7:00 am-12:00 pm	1
blurred vision	slight-mild	2	8:00 am-3:00 pm	1.5
dizziness	slight	2	7:00 am-12:00 pm	1
dizziness	slight	2	8:00 am-2:00 pm	1
dizziness	slight	2	7:00 am-2:00 pm	1
dizziness	slight	2	7:00 am-3:00 pm	1
dizziness	slight	2	morning-late afternoon	1
dizziness	slight	2	morning-late afternoon	1
dizziness	slight	2	morning-late afternoon	1
dizziness	slight	1	1 hour	1
dizziness	slight	1	2 hours	1
dizziness	slight	1	about 1-2 hours	1
dizziness	slight	1	about 1.5 hours	1
dizziness	slight	1	2 hours	1
blurred vision	slight	1	1 hour	1
dizziness	slight	1	2 hours	1
dizziness	slight-mild	2	7.5 hours	1.5
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	2:00 am-8:00 am	2
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	2:00 am-8:00 am	2
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	6:00 am-8:00 am	2
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	6:00 am-8:00 am	2
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	6:00 am-8:00 am	2

Table 2

Fast Dissolving		Slow Dissolving	
Time (Min.)	**% Dissolution**	**Time (Min.)**	**% Dissolution**
0	0.0	0	0.0
15	100	15	30
30	100	30	67
45	100	45	88
60	100	60	95

The cause of the effectiveness of this invention is not known. However, it can be speculated that the dissolution rates called for by the present invention allow the vestibular organs to acclimate themselves to the presence of the minocycline, and thereby avoid unwanted side effects. This explanation is consistent with the avoidance of vestibular side effects even though the use of both slow and fast dissolving dosage forms may achieve the same level of minocycline in the blood stream.

The foregoing example is given by way of illustration only. The scope of the invention is defined only by the following claims.

Claims:

1. A method for reducing the incidence or severity of vestibular side effects resulting from the treatment of acne by the use of oral tetracycline antibiotics, comprising administering the oral tetracycline antibiotic in a slowly dissolving dosage form.

2. The method of claim 1, wherein the oral tetracycline antibiotic is minocycline.

3. The method of claim 2, wherein the antibiotic dissolves at a rate no faster than 15 percent in 15 minutes, 35 percent in 30 minutes, 50 percent in 45 minutes and 80 percent in 60 minutes.

4. The method of the claim 2 wherein the antibiotic dissolves at a rate no faster than 20 percent in 15 minutes, 50 percent in 30 minutes, and 75 percent in 45 minutes.

5. The method of claim 2 wherein and the antibiotic dissolves at a rate no faster than 30 percent in 15 minutes, 60 percent in 30 minutes, and 75 percent in 45 minutes.

6. The method of the claim 2 wherein the antibiotic dissolves at a rate no faster than 35 percent in 15 minutes, 80 percent in 30 minutes, and one hundred percent in 45 minutes.

7. The method of claim 2, wherein the antibiotic dissolves at a rate within the range of 20 to 40 percent in 15 minutes, 50 to 80 percent in 30 minutes, 70 to 95 percent in 45 minutes and 95 to 100 percent in 60 minutes.

8. The method of the claim 2 wherein the antibiotic dissolves at a rate within the range of 25 to 35 percent in 15 minutes, 60 to 80 percent in 30 minutes, and 80 to 100 percent in 45 minutes.

9. The method of claim 2 wherein and the antibiotic dissolves at a rate within the range of 30 to 35 percent in 15 minutes, 65 to 75 percent in 30 minutes, and 90 to 100 percent in 45 minutes.

ABSTRACT

A method for the treatment of acne is provided which results in the reduction of vestibular side effects of oral tetracycline antibiotics.

Attorney Docket No. 98-40012-US

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled METHOD FOR THE TREATMENT OF ACNE the specification of which:

_x_ is attached hereto.

___ was filed on _____ as Application Serial No._____ and was amended on _____ (if applicable).

PCT Application Entering National Phase

___ was filed on _____ as PCT International Application No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)

Attorney Docket No. 98-40012-US

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Serial No.)	(Filing Date)	(Status-patented, pending, abandoned)

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: W. Scott Railton (Reg. No. 23,039); Arland T. Stein (Reg. No. 25,062); Louis M. Heidelberger (Reg. No. 27,899); Frederick H. Colen (Reg. No. 28,061); William J. McNichol, Jr. (Reg. No. 31,179); Mary E. Buckles (Reg. No. 31,907); Francis M. Linguiti (Reg. No. 32,424); Daniel H. Golub (Reg. No. 33,701); Gene A. Tabachnick (Reg. No. 33,801); Kevin J. Garber (Reg. No. 34,171); Gregory L. Bradley (Reg. No. 34,299); John W. Goldschmidt, Jr. (Reg. No. 34,828); Kent E. Baldauf, Jr. (Reg. No. 36,082); Maria N. Rullo (Reg. No. 37,433); R. Anthony Dichl (Reg. No. 38,432); and Cheryl L. Gastineau (Reg. No. 39,469).

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Inventor's Signature Eugene H. Gans Date 2/17/98

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